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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/491,896	01/24/00	DURING	M 102194-6

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EXAMINER	
BUNNER, B	
ART UNIT	**PAPER NUMBER**
1647	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Offic Action Summary	Application No. 09/491,896	Applicant(s) DURING, MATTHEW J.	
	Examiner Bridget E. Bunner	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-85* is/are pending in the application.

4a) Of the above claim(s) *4,13-21,33-35,47-53,55-58,62-67,69 and 77-85* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-12,22-32,36-46,54,59-61,68 and 70-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-85* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachm nt(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 18 June 2001 (Paper No. 11) has been entered in full. Claims 1, 3, 7-8, 26-28, 39-40, 46, 54, and 70-76 are amended.

This application contains claims 4, 13-21, 33-35, 47-53, 55-58, 62-67, 69, and 77-85 drawn to inventions nonelected with traverse in Paper No. 8 (06 December 2000). A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-3, 5-12, 22-32, 36-46, 54, 59-61, 68, and 70-76 are under consideration in the instant application and read upon epilepsy, a peptide vaccine, and a neuroreceptor antigen.

Withdrawn Objections and/or Rejections

1. The objections to the drawings as set forth at pg 3 of the previous Office Action (Paper No. 9, 13 February 2001) are *withdrawn* in view of the submission of formal drawings (Paper No. 11, 18 June 2001).

2. The objections to the specification as set forth at pg 3-4 of the previous Office Action (Paper No. 9, 13 February 2001) are *withdrawn* in view of the amended specification and submission of formal drawings (Paper No. 11, 18 June 2001).

3. The objections to claim 3 as set forth at pg 4-5 of the previous Office Action (Paper No. 9, 13 February 2001) are *withdrawn* in view of the amended claim (Paper No. 11, 18 June 2001).

4. The rejections to claims 1-3, 5-12, 22-32, 36-46, 54, 59-61, 68, 73-74, and 76 under 35 U.S.C. 112, second paragraph, as set forth at pg 7-8 of the previous Office Action (Paper No. 9, 13 February 2001) are *withdrawn in part* in view of the amended claims (Paper No. 11, 18 June 2001). Please see section on 35 U.S.C. 112, second paragraph below.

5. The rejection to claims 1-3, 5-12, 22-32, 36-46, 54, 59-61, 68, and 70-76 under 35 USC § 112, first paragraph, as set forth at pg 5-7 is *withdrawn in part* in view of the amended claims containing the word "pharmaceutical" (Paper NO. 11, 18 June 2001). Please see section on 35 USC §112, first paragraph.

Drawings

6. The formal drawings submitted 18 June 2001 have been received. The drawings will be forwarded to the draftsperson for review at the time of allowance.

Claim Rejections - 35 USC § 112, first paragraph

7. Claims 1-3, 5-12, 22-32, 36-46, 54, 59-61, and 68 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-3, 5-12, 22-32, 36-46, 54, 59-61, and 68 recite a method for treating a subject with epilepsy or at risk of developing epilepsy, a method for treating a neuroendocrine disorder, a method for modifying the function of a target neuroreceptor, and a method for improving cognition comprising administering an amino acid vaccine comprising a therapeutically effective amount of the antigen, NMDAR1, wherein the antigen elicits the production of antibodies.

Applicant's arguments (Paper No. 11, 18 June 2001), as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant argues that the specification need not contain an example if the invention is disclosed in such a manner that one skilled in the art would be able to practice it without undue search burden. Applicant asserts that the specification provides sufficient guidance to the skilled artisan on how to select an appropriate antigen that is capable of eliciting antibodies and how to administer such antigen. Applicant directs Examiner to pg 57-58 in the specification wherein Applicant argues that the skilled artisan would conclude that the epitopes for NMDAR1 are peptide 65 (amino acids 641-657), peptide 49 (amino acids 483-498), peptide 69 (amino acids 691-696), peptide 55 (amino acids 541-566), peptide 72 (amino acids 711-726), and peptide 80 (amino acids 791-807). Furthermore, Applicant asserts that the specification provides ample guidance on how to make and use a peptide vaccine. Applicant states that the dose and effective amount can be determined based on the characteristics of the active compound and that these doses will vary according to the size, sex, and weight of the subject. Applicant also directs the Examiner to pg 26-27 and 33 of the specification where a description of the possible means of antigen peptide administration and preferred route of administration is described. Finally, Applicant asserts that the state of the art at the time the invention was made was such that peptides of NMDAR1, or fusion proteins that contained peptides of NMDAR1, were prepared to generate antibodies. Applicant also cites several abstracts in an attempt to demonstrate that peptide vaccines are used to modify disease states. Applicant asserts that in view of the knowledge in the art and the guidance in the specification, a skilled artisan would be able to make and use the claimed invention without undue experimentation.

Applicant's arguments have been fully considered but are not found to be persuasive because the Applicant has not provided evidence to demonstrate treatment of a subject with epilepsy or with a neuroendocrine disorder by administration of a peptide vaccine comprising an NMDAR1 antigen or an antibody. Applicant has also not provided evidence to demonstrate modification of the function of a target protein in the central nervous system or the improvement of cognition in a subject by administration of a peptide vaccine comprising NMDAR1 antigen or an antibody. The specification teaches the generation of 94 peptides that are 16 amino acids in length as well as possible epitopes for NMDAR1 (pg 57-58). The specification also teaches the presence of circulating NMDAR1 antibodies in rats administered the genetic vaccine (pg 56-57). However, the specification does not teach administration of a NMDAR1 antigen peptide vaccine or antibody to treat a subject with epilepsy or a neuroendocrine disorder. The specification provides no guidance or working examples directed to the administration of a NMDAR1 antigen peptide vaccine or antibody to modify the function of a target protein in the central nervous system in a subject or to improve cognition in a subject. Additionally, the working examples with the genetic vaccine in the specification do not provide guidance regarding treatment of subjects with a protein vaccine. Although the specification discloses the quantity and preferred mode of administration of the peptide vaccine or antibody, one skilled in the art would still not know how to treat epilepsy or a neuroendocrine disorder, modify the function of a protein target, or improve cognition by administration of a peptide antigen vaccine. Undue experimentation would be required of the skilled artisan to determine the efficacy of the peptide vaccine, safety of the vaccine, and the duration of the immunity.

The Examiner recognizes that the state of the art at the time the application was filed demonstrates the preparation of NMDAR1 peptides or fusion proteins with NMDAR1 to generate antibodies. However, as indicated in the previous Office Action (Paper No. 9, 13 February 2001), the state of the art is also such that numerous problems exist in regards to administering a subunit (antigen) vaccine to humans and animals. For example, antigen vaccines have a low level immunogenicity and rapid degradation *in vivo* (Babiuk, L.A. Vaccine 17: 1587-1595, 1999). Applicant asserts that peptide vaccines are used to modify disease states and documents a few representative abstracts. The abstracts cited by the Applicant only relate to amyloid beta peptide vaccination in a transgenic model of Alzheimer's disease. The disorder elected by the Applicant to be treated by a peptide vaccine is epilepsy (Paper No. 8, 06 December 2000). Epilepsy is a neurological disease that is characterized by recurrent seizures. Relevant literature states that successful target-based strategies for drug discovery for epilepsy has been limited because the disorder covers a range of disease states and there are many underlying causes, coupled with the difficulty in identifying the cause in patients and the lack of understanding of the disease (Aiken et al., Frontiers in Bioscience 5: e124-152, 2000; see 3.1). Although the knowledge of peptide vaccines may be known in the art for the treatment of a few diseases, the skilled artisan would not be able to make and use the claimed invention without undue experimentation for the treatment of epilepsy or other neuroendocrine disorder, for the modification of the function of a protein target, or for the improvement of cognition.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary for the treatment of epilepsy and neuroendocrine disorders, modification of the function of a target protein, and the improvement of cognition with

a peptide antigen vaccine or antibody, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the unpredictability of the response and longevity of the antigen vaccine *in vivo* (see discussion and recited reference), undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

New 35 USC § 112, first paragraph rejection

8. Claims 70-76 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising an effective amount of a mouse NMDAR1 antigen capable of eliciting the production of antibodies in the circulatory system of the subject or an amount of an isolated mouse anti-NMDAR1 antibody, does not reasonably provide enablement for a composition comprising a therapeutically effective amount of an antigen capable of eliciting the production of antibodies in the circulatory system of the subject, or a therapeutically effective amount of an isolated antibody, or antibody portion, wherein the antibodies bind to, and modify the function of a target protein in the central nervous system. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 70-76 are directed to a composition comprising a therapeutically effective amount of a neuroreceptor antigen, particularly N-methyl-D-aspartate receptor subunit 1, capable of eliciting the production of antibodies in the circulatory system of the subject or a therapeutically effective amount of an isolated antibody, wherein the antibodies bind to and modify the function of a target protein in the central nervous system. The claims also recite that the antibodies cross the blood-brain barrier and the target protein is an N-methyl-D-aspartate (NMDA) receptor.

The specification teaches that 94 overlapping 16mers are synthesized covering the entire 938 amino acids of the native NMDAR1 protein. Additionally, serum from AAVNMDAR1, AAVlac (control), and naïve rats are screened against the panel of 16mers (pg 57, lines 18-23). Autoantibodies to the receptor are generated and bind to the NMDA receptor which demonstrates specific targeting of a functional domain of the receptor. Also, epitope-mapping analysis demonstrates that the autoantibodies bind to known functional regions of the protein (pg 58). However, the specification does not teach a composition comprising any antigen other than NMDAR1 that is capable of eliciting the production of antibodies in the circulatory system of the subject. Furthermore, the specification does not teach a composition comprising any isolated antibody other than an anti-NMDAR1 antibody. The specification does not teach any composition comprising an antigen or an isolated antibody that modifies the function of any target protein in the central nervous system. Additionally, undue experimentation would be required of the skilled artisan to determine the proper dosage and duration of administration of a therapeutically effective amount of an antigen or antibody necessary to modify the function of a target protein in the central nervous system. The specification does not disclose any guidance as to a "therapeutically effective amount" of an antigen or antibody. The specification also does not disclose any working examples directed to the administration of any antigen or antibody to an animal.

Due to the large quantity of experimentation necessary to determine the dosage and duration of administration of a therapeutically effective amount of an antigen or antibody and to demonstrate a composition comprising an antigen or antibody binds to and modifies the function of a target protein in the central nervous system, the lack of direction/guidance presented in the

specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the unpredictability of the effects of a composition comprising an antigen or an antibody to modify the function of a target protein in the central nervous system, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 USC § 112, second paragraph

9. Claims 9, 29, 41, and 59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Regarding claims 9, 29, 41, and 59, the phrase "or a combination thereof" renders the claims vague and indefinite because it is unclear what particular combinations of vaccines are recited.

Applicant's arguments (Paper No. 11, 18 June 2001), as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant argues that the rejected claims are drawn to a vaccine which can be a viral vector vaccine, a DNA vaccine, a peptide vaccine or a crude antigen vaccine alone or in combination with each other. Applicant also asserts that the vaccine may be a peptide vaccine in combination with a crude antigen vaccine or a viral vector vaccine with a crude antigen vaccine.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, it is not clear how vaccines can be in combination with one another. For example, how can a DNA vaccine and a peptide vaccine combine? Are the vaccines fused? Are the two or more different types of vaccines in the same buffer? If so, is the mode of administration

altered? Or, are they administered separately, but at the same time? Does the "combination" of vaccines target the same cells? (Note, this issue could be overcome by deleting the phrase "or a combination thereof" from the claims.)

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

BEB
Art Unit 1647
August 14, 2001

ELIZABETH KEMMERER
PRIMARY EXAMINER